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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 31/00, 31/135</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/09764</b> <b>(43) International Publication Date:</b> <b>11 May 1994 (11.05.94)</b>
<b>(21) International Application Number:</b> PCT/JP93/01543 <b>(22) International Filing Date:</b> 26 October 1993 (26.10.93) <b>(30) Priority data:</b> 4/310772 27 October 1992 (27.10.92) JP <b>(71) Applicants (for all designated States except US):</b> NIPPON KAYAKU KABUSHIKI KAISHA [JP/JP]; 11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102 (JP). ORION-YHTY-MA OY [FI/FI]; P.O. Box 65, FIN-02101 Espoo (FI). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> ITO, Junpei [JP/JP]; 1090, Kamiochiai, Yono-shi, Saitama 338 (JP). MIYAZAKI, Osamu [JP/JP]; 24-21, Kitazonocho, Kawaguchi-shi, Saitama 333 (JP). EKIMOTO, Hisao [JP/JP]; Takku Puraza 803, 2-11-1, Shimo, Kita-ku, Tokyo 115 (JP). KOYAMA, Michinori [JP/JP]; 2-24-6, Towa, Adachi-ku, Tokyo 120 (JP). SAINO, Tetsushi [JP/JP]; 5-11-14-101, Hachioji, Yono-shi, Saitama 338 (JP). KANGAS, Lauri [FI/FI]; WARRI, Anni [FI/FI]; Orion-yhtymä Oy, P.O. Box 65, FIN-02101 Espoo (FI).		<b>(74) Agents:</b> ASAMURA, Kiyoshi et al.; Room 331, New Ohtemachi Building, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100 (JP). <b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF NON STEROIDAL ANTI ESTROGENS FOR AUTOIMMUNE DISEASES  <b>(57) Abstract</b>  Disclosed is use of nonsteroidal anti-estrogen compounds such as toremifene citrate as active ingredient for treating autoimmune diseases.		

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## DESCRIPTION

## USE OF NON-STEROIDAL ANTIESTROGENS FOR AUTOIMMUNE DISEASES

## 1 [Technical Field]

The present invention relates to use of nonsteroidal anti-estrogen compounds (hereinafter referred to as nonsteroidal anti-estrogens) such as toremifene, expected as a remedy for autoimmune diseases.

The autoimmune diseases include collagen diseases and the like. In light of affected parts by the diseases, there are mentioned, for example, degenerative diseases of supporting tissues and connective tissues; autoimmune degenerative diseases of salivary glands, particularly Sjögren's disease; autoimmune degenerative diseases of kidneys, particularly systemic lupus erythematoses and glomerulonephritis; autoimmune degenerative diseases of joints, particularly rheumatoid arthritis; and autoimmune degenerative diseases of blood vessels such as generalized necrotizing angitis and granulomatous angitis; and multiple sclerosis.

## 20 [Background Art]

Immunosuppressants, nucleic acid antagonists, antimetabolites, etc., are used in the medicinal treatment of autoimmune diseases today. Anti-inflammatory agents, anticoagulants, etc., are also used in the

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1 symptomatic therapies of the diseases. The effects of  
these agents are, however, not yet sufficient.

It is known that the immunosuppressants have  
side effects of provoking diabetes, renal disorders,  
5 infectious diseases, etc. Also the use of the nucleic  
acid antagonist or antimetabolite is frequently  
accompanied by side effects such as hepatic disorders  
and medullary disorders. Thus the medicinal treatment  
of autoimmune diseases is so far very insufficient.

10 It has been demanded to develop a remedy for  
autoimmune diseases which acts on the immune system and  
which has a function mechanism different from that of  
conventional drugs for the diseases and less serious  
side effects.

15 [Disclosure of Invention]

After intensive investigations made for the  
purpose of finding the above-described remedy, the  
present inventors have found that nonsteroidal anti-  
estrogens have an excellent therapeutic effect on the  
20 autoimmune diseases and thus, based on this finding,  
completed the present invention.

The present invention relates to a remedy for  
autoimmune diseases which comprises as active ingredient  
a nonsteroidal anti-estrogen or a pharmaceutically  
25 acceptable salt thereof.

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## 1 [Brief Description of Drawings]

Fig. 1 shows survival times of animals (NZBxNZW F1 mice:B/W F1 mice) which accepted different doses of toremifene.

## 5 [Best Mode for Carrying Out the Invention]

The nonsteroidal anti-estrogen compounds usable in the present invention are those having a triphenyl C<sub>2</sub> - C<sub>5</sub> alkene or triphenyl C<sub>2</sub> - C<sub>5</sub> alkane skeleton. Preferably, they are C<sub>2</sub> - C<sub>5</sub> alkenes or C<sub>2</sub> - C<sub>5</sub> 10 alkanes having three phenyl substituents at the 1-position and 2-position, wherein any of the phenyl groups may have a substituent such as a mono- or di-lower alkyl (C<sub>1</sub> - C<sub>3</sub>) amino lower alkoxy (C<sub>1</sub> - C<sub>3</sub>) group, or a hydroxyl group, or the alkyl group in the above 15 alkenes or alkanes may have a substituent such as a halogen.

Examples of these compounds include toremifene (JP-B-4 19973), tamoxifen (JP-B-59 21861), 4-hydroxy-tamoxifen (JP-A-54 44644), 3-hydroxytamoxifen (JP-A-57 20 122049) and N-demethyltoremifene or 4-hydroxytoremifene (JP-A-3 163015). Toremifene is particularly preferred. It is well-known that these compounds have an anti-neoplastic effect (see Cancer Chemotherapy and Pharmacology, 17, 109-113 (1986) and the above-mentioned 25 patent publications).

The pharmaceutically acceptable salts thereof include, for example, hydrochlorides, sulfates,

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1 citrates, tartrates and phosphates.

Drugs usable in combination with the nonsteroidal anti-estrogens in the medicinal treatment of autoimmune diseases include glucocorticoids (e.g. prednisolone, prednisone, cortisol).. Prednisolone is preferred.

The glucocorticoids themselves have an effect of treating the autoimmune diseases. The nonsteroidal anti-estrogens or a pharmaceutically acceptable salt thereof according to the present invention concomitant with the glucocorticoids synergistically improve the effect of treating.

The remedy of the present invention particularly exhibits an excellent remedial effect on systemic lupus erythematoses.

Therefore the present invention relates to the following:

- (i) a remedy for autoimmune diseases which comprises as active ingredient a nonsteroidal anti-estrogen or a pharmaceutically acceptable salt thereof;
- (ii) a remedy recited in (i), wherein the nonsteroidal anti-estrogen is a compound having a triphenyl C<sub>2</sub>-C<sub>5</sub> alkene or triphenyl C<sub>2</sub>-C<sub>5</sub> alkane skeleton;
- (iii) a remedy recited in (i) or (ii), wherein the active ingredient is toremifene or a pharmaceutically acceptable salt thereof;
- (iv) a remedy recited in (i) or (ii), wherein the autoimmune diseases are collagen diseases, autoimmune

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1 degenerative diseases of kidneys such as nephritis,  
particularly glomerulonephritis, and autoimmune  
degenerative diseases of blood vessels, salivary glands  
and joints;

5 (v) a remedy recited in (i) or (ii), wherein the  
autoimmune diseases are systemic lupus erythematoses;  
and

(vi) a remedy recited in (i) or (ii) for  
concomitant use with a glucocorticoid.

10 The pharmaceutical composition of the present  
invention is administered orally, parenterally or  
intravenously.

Usually, a pharmaceutically effective amount  
of the active ingredient is used in combination with a  
15 suitable medicinal carrier or other auxiliaries. The  
term "pharmaceutically effective amount" herein means an  
amount capable of exhibiting the intended pharmacolog-  
ical activity without causing unfavorable side effects.  
The accurate amount varies in each case depending on  
20 various factors such as administration methods,  
individual natures of the patients and situations in  
which the patient accepts the remedy and, as a matter of  
course, structures of derivatives to be administered.

Dose of the active ingredient for adult is  
25 usually 10 to 1000 mg/day, preferably 20 to 500 mg/day,  
more preferably 30 to 300 mg/day.

In the case of the concomitant use, dose of  
the glucocorticoid for adult is 1 to 100 mg/day,

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1 preferably 2 to 60 mg, and that of the nonsteroidal  
anti-estrogen or the pharmaceutically acceptable salt  
thereof for adult is 10 to 700 mg/day, preferably 20 to  
500 mg/day, more preferably 30 to 300 mg/day.

5 The medicinal carrier or other auxiliaries  
generally usable in combination with the active  
ingredient according to the present invention may be any  
of solid and liquid ones and usually selected in  
consideration of an administration route. Examples of  
10 the solid carrier include lactose, sucrose, gelatin and  
agar, and those of the liquid carrier include water,  
syrup, peanut oil and olive oil. Other suitable  
carriers and auxiliaries known by those skilled in the  
art are also usable. The active ingredient according to  
15 the present invention can be combined with the carrier  
or other auxiliaries to form any of various acceptable  
preparations such as tablets, capsules, suppositories,  
liquid, emulsion and powder.

In the preparations of the remedy of the  
20 present invention, the amount of the nonsteroidal anti-  
estrogen or the pharmaceutically acceptable salt thereof  
can widely vary depending on the preparation, etc.  
Usually, the amount is 0.01 ~ 100% by weight, preferably  
0.1 ~ 70% by weight, and the balance contains the  
25 medicinal carrier or other auxiliaries.

MRL/Mp-lpr/lpr mice spontaneously develop a  
lethal glomerulonephritis, angitis, sialadenitis,  
polyarthrititis, etc., concurrently with the deposition of



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1 an immune complex with age. Therefore, they are widely  
used as experimental models for human systemic lupus  
erythematoses, Sjögren's disease, rheumatoid arthritis  
and autoimmune angitis such as multiple arteritis.

5 The present invention will be explained  
referring to examples on suppression of lymphadenopathy  
glomerulonephritis, angitis, sialadenitis and arthritis  
of MRL/Mp-lpr/lpr mice with the nonsteroidal anti-  
estrogen compound according to the present invention.

10 The nonsteroidal anti-estrogen such as  
toremifene and the pharmaceutically acceptable salt  
thereof according to the present invention exhibit an  
excellent remedial effect on degenerative diseases such  
as autoimmune diseases, for example, systemic lupus  
15 erythematoses.

#### Example 1

Treatment of spontaneous autoimmune diseases of MRL/Mp-  
lpr/lpr mice by administration of 2[4-(Z)-4-chloro-1,2-  
diphenyl-1-butenyl]phenoxy-N,N-dimethylethylamine  
20 citrate (toremifene citrate)

Eight-week old female MRL/Mp-lpr/lpr mice  
(Clea Japan, Inc.) were used in this examination.  
Toremifene citrate (JP-B-4 19973) was suspended in  
carboxymethylcellulose to prepare a 0.5% suspension.  
25 This compound (100 mg/kg) was orally administered to  
each mouse once a day for 13 weeks.

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1 (A) Inhibition of swelling of spleen and lymph  
node of MRL/Mp-lpr/lpr mice with toremifene citrate

Repeated oral administration of 100 mg/kg of  
toremifene citrate once a day for 13 weeks inhibited the  
5 swelling of the spleen and lymph node of each mouse (see  
Table 1).

The spleen and lymph nodes of the MRL/Mp-  
lpr/lpr mice are seriously swollen with age due to the  
presence of the lymphoproliferation gene (lpr). The lpr  
10 codes for the Fas antigen in each mouse. However, in  
the MRL/Mp-lpr/lpr mice, an abnormality of the genes  
disturbs the expression of the Fas antigen. As a  
result, autoreactive T-cells are not subjected to  
negative selection through the Fas antigen in the thymus  
15 and appear in the peripheral tissues to cause the  
swelling of the lymphoid organs and autoimmune symptoms.  
The presence of the autoreactive T-cells was confirmed  
also in the autoimmune diseases of human beings, such as  
rheumatoid arthritis.

20 The results of this study indicated that the  
nonsteroidal anti-estrogen compounds such as toremifene  
citrate are capable of inhibiting the appearance of the  
autoreactive T-cells, thereby suppressing the swelling  
of spleen and lymph node to treat the autoimmune  
25 diseases.

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Table 1: Effect of toremifene citrate<sup>1)</sup> on swelling of spleen and lymph node MRL/Mp-lpr/lpr mice

Group	Number of animals	$\frac{\text{Spleen weight } ^{4)}}{\text{Body weight}}$	$\frac{\text{Lymph node } ^{5)} \text{ weight}}{\text{Body weight}}$
Control <sup>2)</sup>	11	2.34±0.74 <sup>3)</sup>	6.77±1.70
Toremifene citrate treatment	12	1.38±1.06	3.11±1.43

1 1) Toremifene citrate (100 mg/kg) was orally administered to 8-week old mice once a day for 13 weeks.

2) Only 0.5% carboxymethylcellulose was given to the mice of the control group.

5 3) Standard deviation

4)  $\text{Spleen weight/body weight} = \frac{\text{Weight of spleen}}{\text{Body weight of mouse}} \times 100$

5)  $\text{Lymph node weight/body weight} = \frac{\text{Weight of lymph node}}{\text{Body weight of mouse}} \times 100$

(B) Suppression of renal disorder of MRL/Mp-lpr/lpr mouse with toremifene citrate

10 An autopsy was performed on the mice of the control group and the toremifene citrate treated group after the completion of the administration to examine their kidneys pathohistologically. The blood urea nitrogen (BUN) of the serum in each group was examined  
15 to confirm changes in the renal function. As shown in

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- 1 Table 2, toremifene citrate ameliorated the  
glomerulonephritis and healed the renal function in the  
MRL/Mp-lpr/lpr mice.

The glomerulonephritis of the MRL/Mp-lpr/lpr  
5 mice is caused by the deposition of immunocomplexes.  
Also in the case of the autoimmune diseases such as  
systemic lupus erythematoses (SLE) of human, the  
patients suffer from glomerulonephritis concurrent with  
the deposition of the immunocomplex. The results  
10 indicated that the nonsteroidal anti-estrogen compounds  
such as toremifene citrate are effective remedies for  
the degenerative diseases of the kidney, such as the SLE  
with renal syndrome and glomerulonephritis.

Table 2: Improvement of renal function and amelioration  
of glomerulonephritis of MRL/Mp-lpr/lpr mice  
with toremifene citrate

Group	Number of animals	Glomerulonephritis <sup>1)</sup>	BUN (mg/dl) <sup>2)</sup>
Control	11	$2.4 \pm 0.7$ <sup>3)</sup>	43.1 $\pm$ 23.9
Toremifene citrate treatment	12	$1.2 \pm 0.7$	24.6 $\pm$ 4.9

- 1) The kidney was fixed in 10% buffered formalin, and  
15 then paraffin sections thereof were prepared by an  
ordinary method to prepare HE and PAS stained  
specimens. The extent of the disorder of the renal

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1 glomeruli was scored and classified into the following groups:

- 0 (no disorder),
- 1 (slight disorder),
- 5 2 (medium disorder), and
- 3 (heavy disorder).

Twenty-five renal glomeruli were observed for each mouse and the average thereof was calculated.

2) The BUN was determined with a Fuji Dry Chem  
10 Analyzer.

3) Standard deviation.

(C) Inhibition by toremifene citrate of  
sialadenitis, angitis and arthritis of MRL/Mp-lpr/lpr  
mice

15 The salivary gland, renal blood vessel and knee joint of each mouse in the control group and the toremifene citrate treated group were histopathologically examined.

As shown in Table 3, toremifene citrate  
20 prevented the mice from being attacked by sialadenitis, angitis and arthritis.

These results indicated that the nonsteroidal anti-estrogen compounds such as toremifene citrate and tamoxifen citrate can be used as the remedy for  
25 autoimmune sialadenitis (Sjögren's disease), autoimmune arthritis (chronic articular rheumatism) and autoimmune angitis (necrotizing angitis and granulomatous angitis).

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Table 3: Effect of toremifene citrate for preventing MRL/Mp-lpr/lpr mice from being attacked by sialadenitis, angitis and arthritis

Group	Number of animals	Sialadenitis 1)	Angitis 1)	Arthritis 1)
Control	11	2.2±0.6 <sup>2)</sup>	2.1±0.7	1.6±0.9
Toremifene citrate treatment	12	0.9±0.8	0.9±0.8	0.4±0.5

- 1) The salivary gland, kidney and knee joint were fixed in 10% buffered formalin, and then paraffin sections thereof were prepared by an ordinary method to prepare HE and PAS stained specimens. The extent of the disorder was scored and classified into the following groups:

- 0 (no disorder),  
1 (slight disorder),  
2 (medium disorder), and  
3 (heavy disorder).  
2) Standard deviation.

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## 1 Example 2

Effect of concomitant use of toremifene citrate with  
glucocorticoid on MRL/Mp-lpr/lpr mice

Twelve-week old female MRL/Mp-lpr/lpr mice were  
5 used in the examination. Thirty miligrams per kg or 15  
mg/kg of toremifene citrate (TOR) was orally  
administered to each mouse twice a day for 9 weeks from  
the 12th week to the 21st week. A glucocorticoid  
(prednisolone), 8, 4 and 2 mg/kg/day, were subcutaneous-  
10 ly administered to mice once a day as a positive control  
drug. The concomitant use of tremifene with the  
glucocorticoid was also carried out according to the  
same regimen as above. The kidney was taken out from  
each mouse the day after the completion of the whole  
15 administration period and fixed in a PLP fixative.  
Frozen sections were made from the fixed kidney and used  
for an immunostaining with an anti-Mac-2 monoclonal  
antibody (Hybritec Inc., San Diego, USA). The number of  
Mac-2 positive cells (activated macrophages) invading  
20 each of 10 to 20 glomeruli of the kidney, which is  
hereinafter referred to as Mac 2 number, was counted  
under a microscopy to determine an average Mac 2 number  
per glomerulus. The degree of severeness of  
glomerulonephritis was estimated in terms of the average  
25 Mac 2 number (n = 13 for each group). Table 4 shows the  
results.

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Table 4: Suppression of glomerulonephritis of MRL/Mp-lpr/lpr mice by concomitant use of toremifene citrate with glucocorticoid

Group		Mac 2 number
Control		7.5 ± 1.5
Toremifene citrate (TOR)	30 mg/kg	6.2 ± 1.0
	15 mg/kg	6.5 ± 1.2
Prednisolone (P)	8 mg/kg	5.8 ± 0.8
	4 mg/kg	7.9 ± 0.7
	2 mg/kg	9.4 ± 1.0
Control		11.3 ± 1.2
Prednisolone (P)	4 mg/kg	9.1 ± 1.4
	2 mg/kg	7.7 ± 1.0
P 4 mg/kg & TOR 30 mg/kg (concomitant use)		4.1 ± 0.5*
P 4 mg/kg & TOR 15 mg/kg (concomitant use)		4.3 ± 0.5*
P 4 mg/kg & TOR 7.5 mg/kg (concomitant use)		3.5 ± 0.5*
P 2 mg/kg & TOR 30 mg/kg (concomitant use)		3.6 ± 0.7*
P 2 mg/kg & TOR 15 mg/kg (concomitant use)		2.8 ± 0.5*
P 2 mg/kg & TOR 7.5 mg/kg (concomitant use)		4.3 ± 0.6*

\* P &lt; 0.01 (t-test)

- 1 All the groups treated by concomitant use of toremifene citrate (TOR) with prednisolone (P) exhibited significant decrease in Mac 2 number as compared with the control and the prednisolone treated group. On the



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- 1 other hand, the prednisolone treated group and the  
toremifene citrate treated group did not exhibit any  
significant decrease in Mac 2 number as compared with  
the control. The results of these tests indicates that  
5 the concomitant use of the both drugs synergistically  
suppresses the glomerulonephritis.

### Example 3

#### Comparison of survival time

- NZB x NZW mice (B/W F1 mice) were used as a  
10 pathological model of autoimmune diseases (systemic  
lupus erythematoses). Effect of toremifene citrate on  
the survival time of the animals was investigated.

#### Experimental animals:

- F1-hybrids of NZB (female) and NZW (male) mice (B/W F1  
15 mice): Imported from Bomholtgaard, Denmark at the age of  
five weeks.

#### Test groups and doses:

- Control (male): administration polyethyleneglycol (peg)  
3 times a week per os  
20 Control (female): administration peg 3 times a week per  
os

- Toremifene citrate 30 mg/kg/day: administration 70  
mg/kg in polyethylene glycol solution  
3 times a week per os to female  
25 NZB x NZW F1 mice

- Toremifene citrate 3 mg/kg/day: administration 7 mg/kg  
in polyethylene glycol solution 3 times

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1 a week per os to female NZB x NZW F1  
mice

The survival time of the animals in different test groups is presented in Fig. 1. All but two female  
5 control animals have died during the almost two years' follow-up time. Fifty percents of the animals in this group died before/at the age of 40 weeks, and 20% (4/20) were alive after one year.

In the male control group, five animals died  
10 during the first 24 weeks (not shown in Fig. 1) due to aggressive behaviour and thereby acquired infection. These five were excluded from the results. Forty-seven percents of the male control mice are still alive after almost two years' time.

15 In both toremifene treatment groups the life span of the animals has lengthened clearly when compared to the female control animals. In the 3 mg/kg toremifene treatment group only one (1/20) animal had died at/before the age of 40 weeks and three (3/20)  
20 animals in the 30 mg/kg toremifene group.

After one year 80% and 85% of the animals were alive in the 3 mg/kg and 30 mg/kg toremifene treated groups, respectively, which is nearer the percentage of the male control animals ( $\approx 90\%$ ) than that of the female  
25 control group (20%).

Moreover, 25% (5/20) and 10% (2/20) of the animals are still alive after almost two years' time in the lower and higher toremifene dosage group, respec-

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1 tively.

The follow-up data of 60 female and 15 male F1-hybrids of NZB x NZW F1 mice (B/W F1 mice) show that toremifene treatment has clearly extended the life span  
5 of female mice.

## Example 4

Examples of preparations comprising the nonsteroidal anti-estrogen or the pharmacologically acceptable salt thereof as active ingredient will be  
10 given below, which by no means limit the preparations of the present invention.

## Preparation Example 1

Formulation of prepared 200 mg tablet.

	Toremifene citrate	20 mg
15	Starch	85 mg
	Lactose	90 mg
	Magnesium stearate	5 mg

## Preparation Example 2

Formulation of prepared 200 mg tablet.

20	Tamoxifen citrate	20 mg
	Starch	85 mg
	Lactose	90 mg
	Magnesium stearate	5 mg

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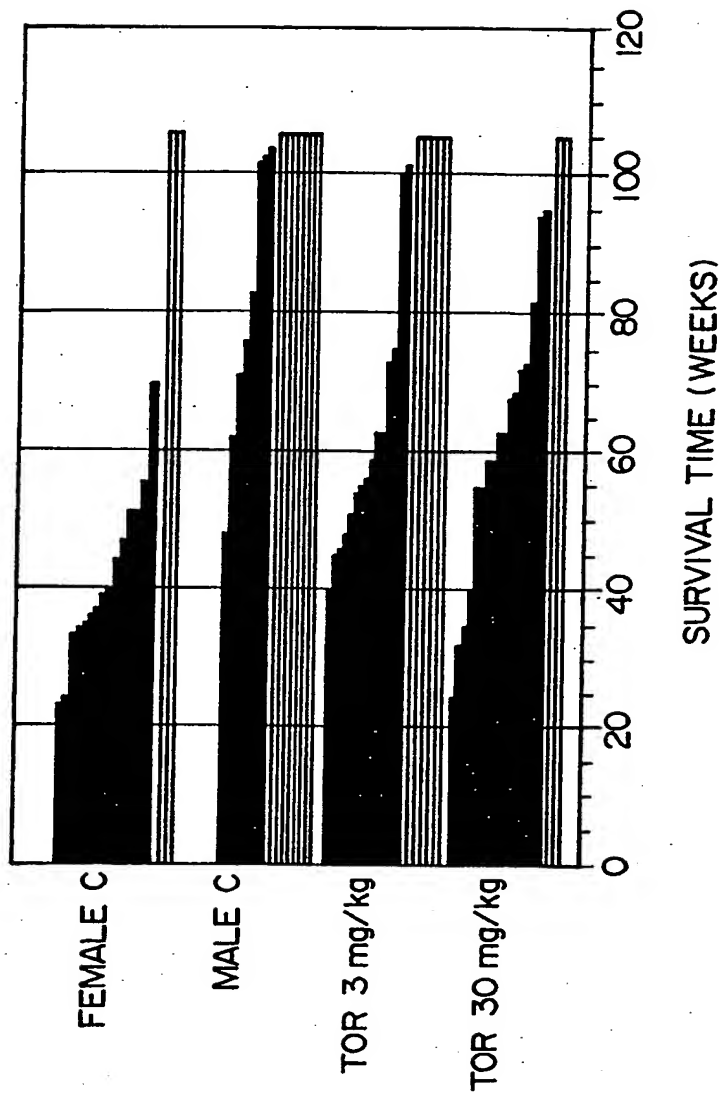
## CLAIMS

1. A remedy for autoimmune diseases which comprises as active ingredient a nonsteroidal anti-estrogen or a pharmaceutically acceptable salt thereof.
2. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen is a compound having a triphenyl C<sub>2</sub>-C<sub>5</sub> alkene or triphenyl C<sub>2</sub>-C<sub>5</sub> alkane skeleton.
3. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen compound is toremifene.
4. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of kidneys.
5. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of salivary glands.
6. A remedy according to claim 1, wherein said autoimmune diseases are autoimmune degenerative diseases of blood vessels.
7. A remedy according to claim 1, wherein said autoimmune diseases are systemic lupus erythematoses.
8. A remedy according to claim 1, wherein said autoimmune diseases are glomerulonephritis.
9. A remedy according to claim 1, wherein said nonsteroidal anti-estrogen compound is toremifene and said autoimmune diseases are autoimmune degenerative diseases of joints.
10. A remedy according to claim 1 for concomitant use with a glucocorticoid.

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FIG. 1



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/JP 93/01543

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 5 A61K31/00 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR. J. DERMATOL. vol. 121, no. 1, 1989 pages 135 - 137 C.J.M. STEPHENS ET AL 'Autoimmune progesterone dermatitis responding to tamoxifen.' see the whole document ---	1,2
X	ANN. DERMATOL. VENEREOL. vol. 188, no. 8, 1991 pages 551 - 555 F. FREYCHET ET AL. 'La dermatose auto-immune a la progestérone.' see the whole document --- -/--	1,2

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Date of the actual completion of the international search

21 December 1993

Date of mailing of the international search report

04.01.94

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## INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/JP 93/01543

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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